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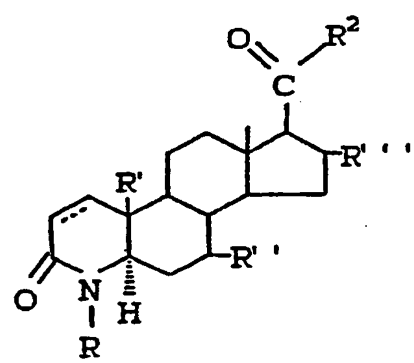
(54) Treatment of patterned alopecia with 17ß-acyl-4-aza-5-androst-1-ene-3-ones and minoxidil

(57) 17β-Acyl-4-aza-5α-androst-1-ene-3-ones of the formula:



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are useful in combination with minoxidil for the treatment of patterned alopecia, e.g., male pattern baldness, female pattern alopecia, alopecia senilis or alopecia areata.

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## TITLE OF THE INVENTION

COMBINATION METHOD FOR TREATING PATTERNED ALOPECIA WITH 17ß-ACYL-4-AZA-5α-ANDROST-1-ENE-3-ONES AND MINOXIDIL

## BACKGROUND OF THE INVENTION

The present invention is concerned with the use of 17ß-acyl-4-aza-5α-androst-1-ene-3-one compounds in combination with minoxidil in treating patterned baldness i.e., male pattern baldness.

Baldness or alopecia, in addition to male pattern alopecia, female pattern alopecia, and alopecia senilis, includes alopecia areta, and further, diseases accompanied by basic skin lesions such as cicatrix or infectious tumors, or accompanied by systemic disorders, for example, an internal secretion abnormality or nutritional disorder.

Also, concerning alopecia areata, it is considered that an autoimmune phenomenon participates

therein, and therefore, the administration of a substance having an immunosuppressive action can have therapeutical effect on alopecia areata.

The causes of human pattern alopecia (also called "androgenic alopecia") and alopecia senilis are considered to be: an activation of male hormones at organs such as hair roots and the sebum gland; a lowering in the amount of blood reaching the hair follicles; a scalp abnormality caused by an excessive secretion of sebum, a formation of peroxides, or a propagation of bacteria; genetic causes; and aging.

Hair revitalizing materials of the prior art generally comprise compounds having the actions of removing or alleviating the causes mentioned above formulated therein. For example, a compound having the action of inhibiting the activation of male hormones, or a compound having the action of increasing the amount of blood reaching the hair follicles, is formulated.

Nevertheless, in human pattern alopecia and alopecia senilis, the epilation mechanism and the hair generation mechanism are very complicated, and by merely inhibiting an activation of male hormones or increasing the amount of blood reaching the hair follicles, as practiced in the prior art, does not sufficiently treat or prevent baldness or alopecia. Accordingly, there is a long-felt need for a hair revitalizing agent for male pattern alopecia and alopecia senilis, which provides satisfactory results.

Patterned baldness is sometimes called androgenic alopecia because male hormones are necessary for its development. It does not occur

before adolescence, nor in castrates. Attempts to prevent alopecia by hormonal treatments by using anti-androgens or female hormones have failed. A hereditary component is also recognized since patterned alopecia runs in families. Despite intensive investigation, the mechanism whereby terminal follicles convert to vellus ones is unknown.

The topical application of minoxidil is currently the most effective therapy for patterned alopecia. Minoxidil is a well-known pharmaceutical agent marketed by The Upjohn Company in the form of LONITEN ® Tablets for the treatment of hypertension. Numerous investigators have demonstrated that it can stimulate visible hair growth in a majority of balding subjects. The structure and use of this compound is described in U.S. Pat. Nos. 4,139,619 and 4,596,812. This compound has varying degrees of efficacy for mederating androgenic alopecia, depending on the degree of baldness, its duration, the age of the patient and, of course, on the concentration of the drug in an appropriate vehicle.

The compound minoxidil (6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine) was approved by the FDA for the treatment of male pattern baldness in August 1988. Minoxidil was recently approved by the FDA for the treatment of female androgenetic alopecia on August 13, 1991. The preparation of minoxidil is described in U.S. Patent Nos. 3,382,247, 3,644,364. Upjohn United States Patents (U.S. Patent Nos. 4,139,619 and 4,596,812) discloses the use of minoxidil in the topical treatment of human baldness. Similarly, an Upjohn

United States Patent (U.S. Patent No. 5,026,691) discloses the use of minoxidil and an antiinflammatory agent for the treatment of of human baldness. Japanese patent Kokai 61-260010 states that topical minoxidil formulations containing other specified agents may be prepared.

It is also well known in the art that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, and male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system.

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5α-dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5α-reductase. It is also known that inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation. For example, a number of 4-aza steroid compounds are known which are 5-alpha reductase inhibitors. See, for example, U.S. Pat. Nos. 2,227,876; 3,239,417; 3,264,301; and 3,285,918; French Pat. No. 1,465,544; Doorenbos and Solomons, J. Pharm. Sci. 62, 4, pp. 638-640 (1973); Doorenbos and Brown, J. Pharm. Sci., 60 8, pp. 1234-1235 (1971); and Doorenbos and Kim, J. Pharm. Sci. 63, 4, pp. 620-622 (1974).

In addition, U.S. Patents 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J.

Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson et al., U.S. Patent 4,845,104 to Carlin et al. and U.S. Patent 4,732,897 to Cainelli et al. describe 4-aza-17β-substituted-5α-androstan-3-ones which are said to be useful in the treatment of DHT-related hyperandrogenic conditions.

Further described in the field are the following two prior art references:

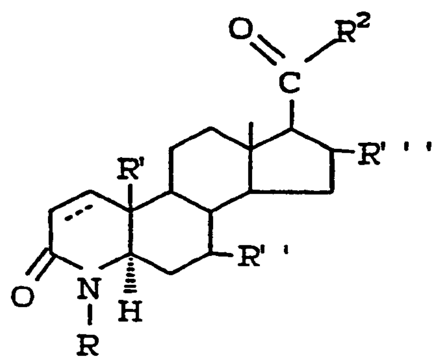
Proc. Natl. Acad. Sci, USA, Vol. 87, pp. 3640-3645, May 1990 by S. Andersson and D.W. Russell which describes structural and biochemical properties of cloned and expressed human and rat steroid 5-alpha reductases; and

Nature, Vol 354, Nov. 1991, pp 159-161 by S. Andersson, et al., which describes the isolation of a second human enzyme, 5-alpha reductase 2, and the effect of a deletion in this gene in male pseudohermaphroditism.

The topical application of minoxidil has met with limited success. What is desired in the art is an improved formulation of minoxidil for treating patterned alopecia.

DESCRIPTION OF THE INVENTION

The present invention is concerned with a method for treating patterned alopecia which comprises the concomitant administration of a therapeutically effective amount of (A): a 17ß-acyl-4-aza-5α-androst-1-ene-3-one compound of the formula:



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wherein the dotted line represents a double bond when present;

R is selected from hydrogen, methyl and ethyl;

$R^2$ is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of $C_1$-$C_2$ alkyl or halo;

(b) an aralkyl radical selected from benzyl or phenethyl;

(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, -O$C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkyl, halo or nitro;

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, $-OC_1-C_4$ alkyl, $C_1-C_4$ alkyl, $-(CH_2)_mOH$, $-(CH_2)_n$, COOH, including protected hydroxy, where m is 1-4, n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, $-SC_1-C_4$ alkyl, $-SOC_1-C_4$ alkyl, $-SO_2C_1-C_4$ alkyl, $-SO_2N(C_1-C_4\text{-alkyl})_2$, $C_1-C_4$ alkyl $-(CH_2)_mSH$, $-S-(CH_2)_n-O-COCH_3$, where m is 1-4 n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above sulfur containing radicals is present;

(3) $N(R^3)_2$, which can be protected, where $R^3$ is independently H or $C_1-C_4$ alkyl, where the monoaryl ring can also be further substituted with $C_1-C_4$ alkyl; and

(4) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;

and R', R'' and R''' are each selected from hydrogen and methyl, and pharmaceutically acceptable salts thereof, administered systemically, topically or orally and (B) minoxidil, administered topically.

A preferred embodiment of the compounds of our invention process is:

the compound of above Structure I,
wherein the dotted line is a double bond,
R is hydrogen or methyl, and
$R^2$ is branched chain alkyl, or cycloalkyl of from 4-10 carbons, and R'' and R''' are hydrogen.

Another embodiment of the invention is the compounds of above Structure I where $R^2$ is phenyl, or phenyl substituted by substituents described above, including where
$R^2$ is phenyl, 2-, 3-, or 4-tolyl, xylyl, 2-bromophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 2,6-dibromophenyl, aminophenyl, N-alkylaminophenyl, N-N-dialkylaminophenyl, 4-biphenyl, 3-biphenyl, naphthyl, anthracyl, phenanthryl, thiophenyl, methylthiophenyl, methylsulfinyl, phenyl, methylsulfophenyl, aminosulfophenyl, thioethylphenyl, acetoxymethylthiophenyl, 17ß-(4-hydroxyphenyl), 17ß-(3-hydroxyphenyl), 17ß-(3,4-dihydroxyphenyl), or 17ß-(3,5-dimethyl-4-hydroxyphenyl).

Representative compounds of the invention are:

17ß-(phenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(2-tolylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(3-tolylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17β-(4-tolylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17β-(2-bromophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17β-(2-chlorophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17β-(2,6-dichlorophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17β-(2,6-dibromophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17β-(xylylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17β-(t-butylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(isobutylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(isooctylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(n-octylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(1,1-diethylbutylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(neopentylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(tert-amylcarbonyl)-4-aza-4-5α-androst-1-ene-3-one;
17β-(tert-hexylcarbonyl)-4-aza-4-5α-androst-1-ene-3-one;
17β-(cyclohexylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(cyclopentylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(benzylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(2-pyridylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(4-pyridylcarbonyl)-4-aza-5α-androst-1-ene-3-one;
17β-(2-pyrrolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2-furylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2-thiophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2-adamantylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(phenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2-tolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(3-tolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(4-tolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2-bromophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2-chlorophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2,6-dichlorophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(2,6-dibromophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(xylylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17β-(phenylethyl)carbonyl-4-aza-5α-androst-1-ene-3-one;

17β-(4-dimethylaminophenylcarbonyl)-4-aza-5a-androst-1-en-3-one;

17β-(3-dimethylaminophenylcarbonyl)-4-aza-5a-androst-1-en-3-one.

17β-(3,4-diethylaminophenylcarbonyl)-4-aza-androst-1-en-3-one.

17β-(3,5-dimethyl-4-diethylaminophenylcarbonyl)-4-aza-5a-androst-1-en-3-one;

17β-(4-N-methylaminomethylphenylcarbonyl)-4-aza-5a-androst-1-en-3-one; or

17β-(2-N-ethylamino-4-ethylphenylcarbonyl)-4-aza-5a-androst-1-en-3-one.

17ß-(4-phenylbenzoyl)-4-aza-5a-androst-1-en-3-one;
17ß-(3-phenylbenzoyl)-4-aza-5a-androst-1-en-3-one;
17ß-(4-biphenyl)-4-aza-5a-androst-1-en-3-one;
17ß-(3-biphenyl)-4-aza-5a-androst-1-en-3-one;
17ß-(1-naphthyl)-4-aza-5a-androst-1-en-3-one;
17ß-(2-naphthyl)-4-aza-5a-androst-1-en-3-one;
17ß-(1-phenanthryl)-4-aza-5a-androst-1-en-3-one;
17ß-(2-phenanthryl)-4-aza-5a-androst-1-en-3-one;
17ß-(1-biphenyl)-4-aza-5a-androst-1-en-3-one;
17ß-(9-anthracyl)-4-aza-5a-androst-1-en-3-one;
17ß-(4-thiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(3-thiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(4-methylthiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(4-methylsulfinylphenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(4-methylsulfophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(3-methylsulfinylphenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(4-N,N-dimethylaminosulfophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(2-ethyl-4-methylthiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;
17ß-(4-thioethylphenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;
17ß-(4-acetoxymethylthiophenylcarbonyl)-4-aza-4-methyl5α-androst-1-en-3-one;
17ß-(2-methyl-4-methylthiophenylcarbonyl)-4-aza-4-m thyl-5α-androst-1-en-3-one;

17ß-(2-methyl-4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(2-isopropyl-4-methylsulfophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-methylthiophenylcarbonyl)-4-aza-4-methyl-5α-androstan-3-one;

17ß-(4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5α-androstan-3-one;

17ß-(4-methylsulfophenylcarbonyl)-4-aza-4-methyl-5α-androstan-3-one;

17ß-(4-hydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3-hydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3,4-dihydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-hydroxymethylphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(2-hydroxyethylphenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-methoxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-carboxymethylphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-hydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(3-hydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(3,4-dihydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-hydroxymethylphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

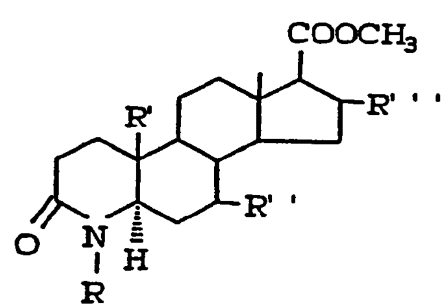
17ß-(2-hydroxyethylphenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-methoxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-carboxymethylphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one; and

17ß-(4-carboxyphenyl)-4-aza-5α-androst-1-en-3-one, and the corresponding compounds wherein the 4-hydrogen substituent is replaced in each of the above named compounds by a methyl or an ethyl radical.

The compounds of formula I of the present invention are prepared by a method starting with the known steroid ester of the formula:




named 17ß-(carbomethoxy)-4-aza-5α-androstan-3-one, which includes the stages of (1) dehydrogenating said starting material to produce the corresponding compound containing a double bond in the 1,2-position of the A-ring, (2) converting the 17-carbomethoxy substituent into a 17ß-acyl substituent and, if desired (3)

alkylating the A-ring nitrogen to introduce 4-methyl or 4-ethyl substituents into the A-ring. For the dehydeogenation step, it is preferable that the 4-aza nitrogen be unsubstituted, The dehydrogenation step can be carried out, e.g. according to the procedure of Dolling, et al. involving dichlorodicyanobenzoquinone, JACS (1988) Vol. 110, pp. 3318-3319. Stage (2) may consist of one or more chemical steps and if desired may take place before stage (1) or following stage (1) or stage (3).

In accordance with the process of the present invention, the products of our invention are formed by (1) heating a 17ß-alkoxycarbonyl-4-aza-5α-androstan-3-one compound III with a dehydrogenating agent such as benzeneseleninic anhydride in refluxing chlorobenzene to form a 17ß-alkoxycarbonyl-4-aza-5α-androst-1-en-3-one (IV), (2) the formed 5α-androst-1-en-3-one compound from step (1) is reacted with sodium hydride and under anhydrous conditions in a neutral solvent such as dimethylformamide, (2) contacting the resulting reaction mixture with an alkyl (methyl or ethyl) iodide to form the corresponding 17ß-alkoxycarbonyl-4-alkyl-4-aza-5α-androst-1-en-3-one (V), (3) subsequently hydrolyzing said 17ß-alkoxycarbonyl-4-alkyl-4-aza-5α-androst-1-en-3-one with a strong base such as aqueous methanolic potassium hydroxide at the reflux temperature, followed by acidification and isolation of the resulting steroidal acid, 17ß-carboxy-4-alkyl-4-aza-5α-androst-1-en-3-one (VI), (4) said steroidal acid is then converted to its corresponding 2-thiopyridyl ester by

refluxing with triphenyl phosphine and 2,2'-dipyridyl disulfide in an inert solvent and the product 17ß-(2-pyridylthiocarbonyl)-4-alkyl-4-aza-5α-androst-1-en-3-one (VII) is isolated by chromatography on silica, (5) said pyridylthio ester is then reacted with an $R^2$-Li or an $R^2MgX$ (X=Cl, Br) compound, such as sec-butylmagnesium chloride in tetrahydrofuran, to form the desired product, e.g., 17ß-(sec-butylcarbonyl)-4-alkyl-4-aza-5α-androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel. When the previous reaction is carried out using an $R^2MgX$ or, an $R^2$-Li compound in place of sec-butylmagnesium chloride, the corresponding 17ß-(acyl)-4-alkyl-4-aza-5α-androst-1-en-3-one is prepared wherein acyl is $R^2$ carbonyl.

In accordance with the process of our invention, the corresponding 17ß-acyl-4-aza-5α-androst-1-en-3-one XV is readily prepared from the 17ß(alkoxycarbonyl)-4-aza-5α-androsten-3-one (IV) by repeating the above series of reaction steps but omitting step 2 hereinabove, i.e., treatment of the 4-aza-5α-androst-1-en-3-one with sodium amide followed by methyl or ethyl iodide.

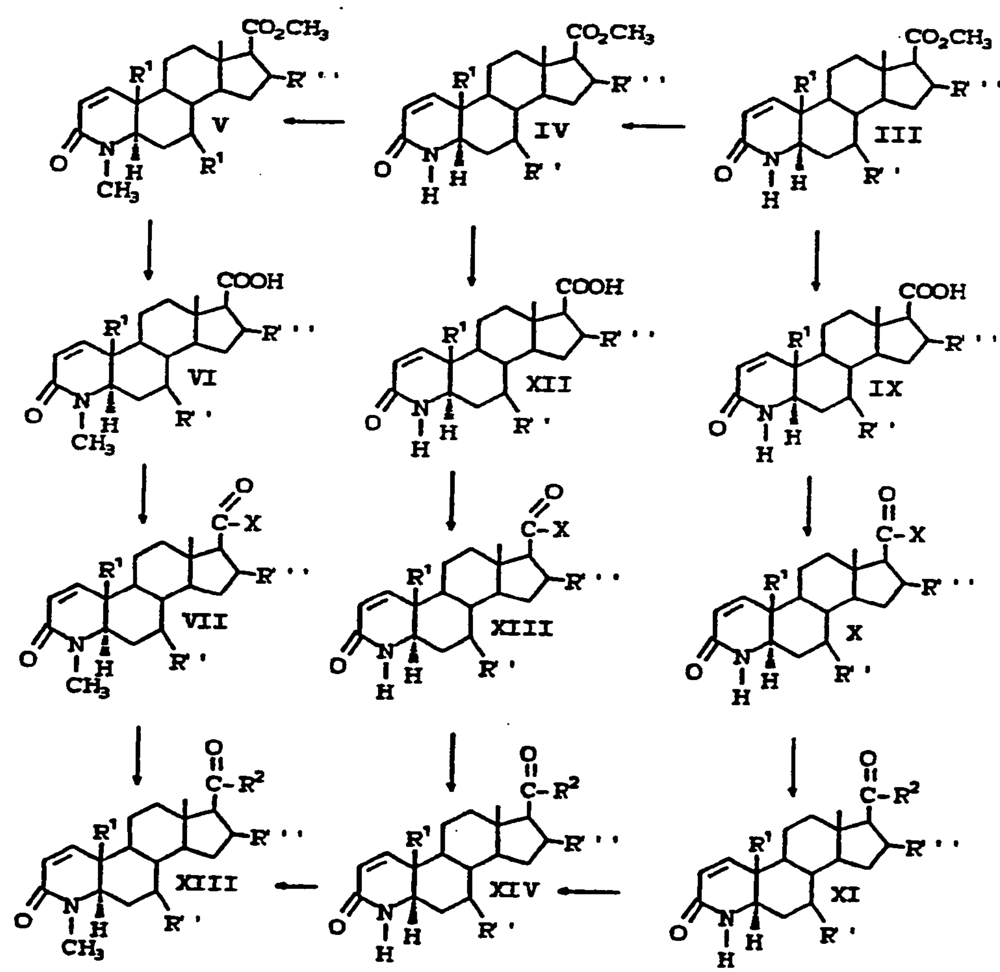
In accordance with a further alternate process of preparing the compounds of our invention, having only hydrogen as the sole substituent on the ring A-nitrogen, the 1,2-double bond in the A-ring is introduced as the last step of the process. Thus, a 17ß-alkoxycarbonyl-4-aza-5α-androstan-3-one (III) is hydrolyzed to the corresponding steroidal acid, 17ß-carboxy-4-aza-5α-androstan-3-one, (IX) which, in turn, is convert d to the corresponding thiopyridyl

ester, 17ß-(2-pyridylthiocarbonyl)-4-aza-5α-androstan-1-one (X) followed by treatment of the ester with an $R^2MgX$ or $R^2Li$ compound wherein $R^2$ is as defined hereinabove to form a 17ß-(acyl)-4-aza-5α-androstan-3-one (XI) which is dehydrogenated as previously described to produce compound XIV, 17ß-(acyl)-4-aza-5α-androst-1-en-3-one.

In an additional alternative process for making the compounds of formula I when the starting material is an ester, particularly methyl ester as shown in formula III-V in the schematic, reaction with a Grignard reagent $R^2MgX$, gives the ketone, 17ß-$R^2$CO-, corresponding to the $R^2$ moiety associated with the Grignard reagent.

The 16-methyl derivative wherein R''' is methyl are prepared from known 16-methyl-17-acyl-4-methyl-4-aza-5α-androstan-3-ones, e.g. 4,16ß-dimethyl-17ß-acetyl-4-aza-5α-androstan-3-one by known dehydrogenation procedures for 4-methyl-4-aza compounds to produce the corresponding 4,16ß-dimethyl-17ß-acetyl-4-aza-5α-androst-1-en-3-one.

The above reactions are schematically represented in the following structural outline:



X is 2-pyridylthio

wherein X is a 2-pyridylthio substituent and $R^2$ is defined as hereinabove.

In the above described reaction Scheme, where $R^2$ is p-hydroxybiphenyl, this can be derived by starting with an appropriate bromobiphenylylphenol, e.g. p-bromobiphenylphenol, protecting the phenolic -OH with a conventional blocking group, e.g. trioganosilyl, i.e. t-butyldimethylsilyl, carrying out the Grignard reaction and then deblocking the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to one skilled in the art from this disclosure.

By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Preferred are the triorganosilyl groups, e.g. t-butyldimethylsilyl, phenyldimethylsilyl, diphenylmethylsilyl, and the like.

By the term "$C_1$-$C_4$ alkyl" is used herein, is meant linear or branched alkyl, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl.

When this reaction scheme is carried out using an $R^2MgX$ or $R^2$-Li compound containing an thiophenyl substituted $R^2$, e.g. p-methylthiophenyl magnesium chloride, the corresponding 17ß-

(substituted thio-benzoyl)-4-alkyl-4-aza-5α-androst-1-en-3-one is prepared wherein phenyl is $R^2$.

The Grignard reagent, $R^2MgX$, for all the species included within the scope of this invention, are available or can readily be made by one skilled in the art. For example, where $R^2$ is $C_1$-$C_4$ alkyl thiophenyl, can be formed from the appropriate $C_1$-$C_4$ alkyl thiobromobenzene, e.g. p-methylthiobromobenzene.

The formed $C_1$-$C_4$ alkyl thiobenzene can be used to further prepare $C_1$-$C_4$ alkyl sulfoxides by oxidation with e.g. m-chloroperbenzoic acid. The resulting sulfoxide can be further oxidized by the use of the m-chloroperbenzoic acid reaction to proceed for a longer period of time to form the $C_1$-$C_4$ alkyl sulfone.

Further, the sulfoxide can be used in the Pummerer rearrangement to form the corresponding thiol.

The $-SO_2N(C_1$-$C_4$ alkyl$)_2$ substituted phenyl ($R^2$) is formed from the appropriate bromobenzene, e.g. p-N,N-dimethylaminosulfobromobenzene which is used directly in the Grignard reaction to form the final product.

The thioalkyl groups on the phenyl ring, i.e. $-(CH_2)_mSH$, where m is 1-4, are readily formed via a four step procedure from an alkoxy alkyl phenyl bromide, $Br-C_6H_4-(CH_2)_mOCH_3$. Direct addition of the Grignard reagent prepared from above-bromoalkyl phenyl derivative to the thiopyridyl ester results in the keto derivative, i.e. 17ß(4-methoxyalkyl-benzoyl)-4-aza-5α-androst-1-ene-3-one. This can be readily converted into thio analogue via $BBr_3$ at

$-70°C$ to form the hydroxyalkyl derivative, followed by displacement by halogen, e.g. bromo and then converting the halogenated compound through NaSH displacement to give the final mercapto compound. Where in the Reaction Scheme said pyridylthio ester is reacted with an aminophenyl containing $R^2$-Li or an $R^2MgX$ (X=Cl, Br) compound, such as p-dimethylaminophenyl magnesium chloride, this is carried out in tetrahydrofuran to form the desired product 17ß-(p-dimethylaminophenyl-carbonyl)-4-alkyl-4-aza-5a-androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel.

The Grignard reagent, $R^2MgX$, for all of the aminophenyl species included within the scope of this invention, are available and can be made readily by one skilled in the art.

Where in the process said Grignard reagent contains a phenolic type $R^2$ moiety, then said pyridylthio ester is then reacted with an $R^2$-Li or an $R^2MgX$ (X=Cl, Br) Grignard reagent, such as p-methoxyphenyl-magnesium chloride in tetrahydrofuran to form the desired product, e.g. 17ß-(p-methoxyphenylcarbonyl)-4-alkyl-4-aza-5α-androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel. When this reaction is carried out using another $R^2MgX$ or, an $R^2$-Li compound in place of p-methoxyphenylmagnesium chloride, the corresponding 17ß-(substituted benzoyl)-4-alkyl-4-aza-5α-androst-1-en-3-one is prepared wherein phenyl is $R^2$.

The Grignard reagent, $R^2MgX$, for all of the species included within the scope of this invention, are available and can be made readily by one skilled in the art.

For example, where $R^2$ is hydroxyphenyl, this can be derived by starting with an appropriate bromophenol, e.g. p-bromophenol, protecting the phenolic -OH with a conventional blocking group, e.g. trioganosilyl, i.e. t-butyldimethylsilyl, carrying out the Grignard reaction and then deblocking the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

For $R^2$ being hydroxyethylphenyl, the same blocking procedure can be analogously conducted starting with the appropriate hydroxyalkyl bromophenol, e.g. p-hydroxymethylbromobenzene, or p-hydroxyethylbromobenzene.

Where $R^2$ is carboxyphenyl, this can be obtained by the chromic acid oxidation of the appropriate hydroxymethylbenzene, e.g. p-bromo-hydroxymethylbenzene, formed as described above.

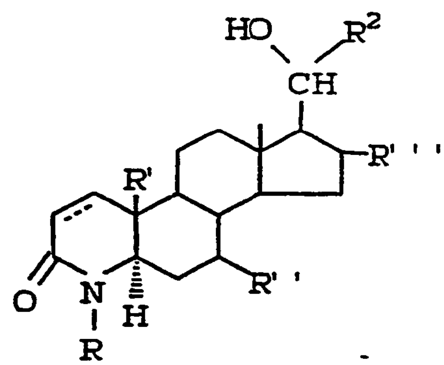
Where $R^2$ is $-O-C_1-C_4$ alkyl, the appropriate bromo-$O-C_1-C_4$ alkyl benzene, e.g. p-methoxybromobenzene, is utilized for the Grignard reaction.

Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to one skilled in the art from this disclosure.

By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH groups which can be protected by conventional

blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Preferred are the triorganosilyl groups, e.g. t-butyldimethylsilyl, phenyldimethylsilyl, diphenylmethylsilyl, and the like.

Also within the scope of the present invention is the use of ketone reduction products of I, in combination with minoxidil for treatment of patterned alopecia, being secondary alcohols of the formula:



wherein R is selected from hydrogen, methyl and ethyl;

$R^2$ is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of $C_1$-$C_2$ alkyl or halo;

(b) an aralkyl radical selected from benzyl or phenethyl;

(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, $-OC_1-C_4$ alkyl, $C_1-C_4$ alkyl, halo or nitro;

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, $-OC_1-C_4$ alkyl, $C_1-C_4$ alkyl, $-(CH_2)_mOH$, $-(CH_2)_n$ COOH, including protecting hydroxy, where m is 1-4, n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, $-SC_1-C_4$ alkyl, $-SOC_1-C_4$ alkyl, $-SO_2C_1-C_4$ alkyl, $-SO_2N(C_1-C_4\text{-alkyl})_2$, $C_1-C_4$ alkyl $-(CH_2)_mSH$, $-S-(CH_2)_n-O-COCH_3$, where m is 1-4 n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above sulfur containing radicals is present;

(3) $N(R^3)_2$, which can be protected, where $R^3$ is independently H or $C_1-C_4$ alkyl, where the monoaryl ring can also be further substituted with $C_1-C_4$ alkyl; and

(4) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;

R', R'' and R''' are hydrogen or methyl, wherein the dotted line represents a double bond which can be present, and pharmaceutically acceptable salts and esters thereof.

These compounds can be made by conventional sodium borohydride reduction of the carbonyl attached to $R^2$ without reducing the amide carbonyl in Ring A or the 1,2-double bond, if present. If the $R^2$ phenyl contains a carbonyl function, it can be selectively blocked and then regenerated after the borohydride reduction by conventional methods.

The borohydride reduction can be carried out in, e.g. water or aqueous methanol, at a temperature of room temperature to 50°C and the product then isolated and purified by conventional means. The compounds are also active as 5-alpha reductase inhibitors in the treatment of patterned alopecia.

The compounds of the present invention, prepared in accordance with the method described above, are, as already described, potent agents in combination with minoxidil for the treatment of patterned alopecia.

The compounds of Formula I may be employed in a pharmaceutical composition additionally comprising: Minoxidil, or a pharmaceutically acceptable salt thereof. The compositions are useful in hair revitalizing, such as in the treatment of male pattern alopecia, female pattern alopecia, alopecia senilis or alopecia areata, by providing epilation prevention, hair germination, and/or a promotion of hair generation and hair growth.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. For example, the compounds of Formula I and minoxidil may be utilized with hydroxypropyl methylcellulose essentially as described in U.S Patent No. 4,916,138, issued April 10, 1990, or with a surfactant essentially as described in EPO Publication 0,428,169. Dosage forms for external application may be prepared essentially as described in EPO Publication 0,423,714 or in U.S. Patent No. 4,938,953. The active object compounds are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For the treatment of these conditions and diseases a compound of Formula I may be administered in combination with prior to, concurrent to, or subsequent to the administration of minoxidil. Such compounds may be administered orally, topically, or parenterally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. However, the preferred mode of administration is topically. It is especially preferred that the hair revitilizing composition of the present invention is administered by a percutaneous administration or by spraying onto the skin.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For external administration the compound of Formula I may be formulated within the range of, for example, 0.0001% to 60% by weight, preferably from 0.001% to 10% by weight, and most preferably from about 0.005% to 0.8% by weight. In general, the percutaneous dose of the compound of Formula I for a human being per day/per person is preferably 1 to 2000 mg, more preferably 1 to 20 mg, per day/per person.

For external administration, minoxidil may be formulated in the composition within the range of, for example, 1% to 5% by weight, and preferably from 2% to 4% by weight.

In addition, the compositions of the present invention may be administered on an intermittent basis; i.e. at semidaily, daily, semiweekly, weekly, semi-monthly or monthly intervals.

It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the instant invention.

## EXAMPLE A

A lotion comprising the composition shown below may be prepared.

| Ingredient | (weight %) |
|---|---|
| 95% Ethanol | 80.0 |
| Compound of Formula I | 3.0 |
| Minoxidil | 2.0 |
| α-Tocopheral acetate | 0.01 |
| Ethylene oxide (40 mole) adducts of hardened castor oil | 0.5 |
| Purified water | 14.0 |
| perfume and dye | q.s. |

Into 95% ethanol are added a compound of Formula I, minoxidil, α-tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye, and the mixture is stirred and dissolved, followed by an addition of purified water, to obtain a liquid lotion.

## EXAMPLE B

An emulsion is prepared from A phase and B phase having the following compositions.

| (A phase) | (weight %) |
|---|---|
| Whale wax | 0.5 |
| Cetanol | 2.0 |
| Petrolatum | 5.0 |
| Squalane | 10.0 |
| Polyoxyethylene (10 mole) monostearate | 2.0 |
| Sorbitane monooleate | 1.0 |
| Compound of Formula I | 0.01 |
| Minoxidil | 0.5 |

| (B phase) | (weight %) |
|---|---|
| Glycerine | 10.0 |
| Purified water | 68.5 |
| Perfume, dye, and preservative | q.s. |

The A phase and the B phase are respectively heated and melted and maintained at 80°C, both phases are mixed to be emulsified, and are cooled under stirring to normal temperature to obtain an emulsion.

## EXAMPLE C

A cream is prepared from A phase and B phase having the following compositions.

| (A phase) | (weight %) |
|---|---|
| Fluid paraffin | 5.0 |
| Cetostearyl alcohol | 5.5 |
| Petrolatum | 5.5 |
| Glycerine monostearate | 3.0 |
| Polyoxyethylene (20 mole) 2-octyldodecyl ether | 3.0 |
| Propylparaben | 0.3 |

| (B phase) | (weight %) |
|---|---|
| Compound of Formula I | 0.8 |
| Minoxidil | 1.0 |
| Glycerine | 7.0 |
| Dipropylene glycol | 20.0 |
| Polyethylene glycol 4000 | 5.0 |
| Sodium Hexametaphosphate | 0.005 |
| Purified water | 43.895 |

The A phase is heated and melted, and maintained at 70°C, the B phase is added to the A phase followed by stirring, and the obtained emulsion is cooled to obtain a cream.

## EXAMPLE D

A hair liquid comprising the composition shown below may be prepared.

| Ingredient | (weight %) |
|---|---|
| Polyoxyethlene butyl ether | 20.0 |
| Ethanol | 50.0 |
| Compound of Formula I | 1.0 |
| Minoxidil | 1.0 |
| Propylene glycol | 5.0 |
| Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts) | 0.4 |
| Perfume | q.s. |
| Purified water | q.s. |

Into ethanol is added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a compound of Formula I, minoxidil, and perfume, which are mixed under stirring, and to the mixture is added purified water, to obtain a hair liquid.

EXAMPLE E

A hair shampoo comprising the composition shown below may be prepared.

| Ingredient | (weight %) |
|---|---|
| Sodium laurylsulfate | 5.0 |
| Triethanolamine laurylsulfate | 5.0 |
| Betaine lauryldimethylaminoacetate | 6.0 |
| Ethylene glycol distearate | 2.0 |
| Propylene glycol | 5.0 |
| Compound of Formula I | 1.0 |
| Minoxidil | 2.0 |
| Ethanol | 2.0 |
| Perfume | 0.3 |
| Purified water | 71.7 |

Into 71.1 g of purified water is added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethylamino acetate, then a mixture obtained by adding 1.0 g of a compound of Formula I, 2.0 g of minoxidil, 5.0 g of polyethylene glycol, and 2.0g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume, is successively added, and the mixture is heated then cooled to obtain a hair shampoo.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encom-

passes all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

Accordingly, the present invention is also particularly concerned with providing a method of treating patterned alopecia by parenteral or oral administration, of the compounds of the present invention.

The compositions containing the compounds of Structure I the present invention as the active ingredient for use in the treatment of patterned alopecia can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of tablets, capsules, solutions, or suspensions, of by intravenous injection. The daily dosage of the products may be varied over a wide range varying from about 1 to 2,000 mg per person. The compositions are preferably provided in the form of scored tablets containing 0.1, 1, 5, 10, 25, 50, 100, 150, 250, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg to about 50 mg/kg of body weight per day. This translates to a daily dosage of from 0.1 mg to 2000 mg, preferably 1 to 20 mg per person. Preferably the range is from about 1 mg to 7 mg/kg of body weight per day. These dosages are well below the toxic dose of the product. Capsules containing

the product of this invention can be prepared by mixing an active compound of the present invention with lactose and magnesium stearate, calcium stearate, starch, talc, or other carriers, and placing the mixture in gelatin capsule. Tablets may be prepared by mixing the active ingredient with conventional tableting ingredients such as calcium phosphate, lactose, corn starch or magnesium stearate. The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methylcellulose and the like. Other dispersing agents which may be employed include glycerin and the like. For parenteral administration sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservative are employed when intravenous administration is desired.

For the treatment of patterned alopecia the compounds of the present invention can also be administered in the formula of pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical administration. These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

The method of preparing the compounds of the present invention, already described above in general terms, may be further illustrated by the following examples.

## EXAMPLE 1

Methyl 3-oxo-4-aza-5a-androst-1-ene-17ß-carboxylate

A suspension of 83.7 g of methyl 3-oxo-aza-5a-androstane-17-carboxylate* and 126.5 g of benzeneseleninic anhydride in 2.09 l of chlorobenzene was heated at reflux for 2 hours. The reflux condenser was switched to a distillation head and the mixture was distilled slowly to remove water that had formed in the reaction (2 hours). The solution was evaporated to leave 198 g of wet residue. The residue as a solution in dichloromethane was washed with saturated aqueous $NaHCO_3$ solution and saturated NaCl solution, then dried and evaporated to leave 172.4 g. This material was chromatographed on 2.56 kg of silica gel eluting first with dichloromethane (5 liters) and then with 4:1 dichloromethane-acetone. The desired product was eluted with 8 liters of the above-mixed solvent and evaporated to dryness *in vacuo* to yield 53.4 g solid. It was washed with diethyl ether and dried to leave 49.5 g of the above-titled product, m.p. 278-280°C.

*Rasmusson Johnston and Arth. U.S. Patent 4,377,584, March 22, 1983.

EXAMPLE 2

S-(2-Pyridyl)-3-oxo-4-aza-5α-androst-1-ene-17β-thiocarboxylate

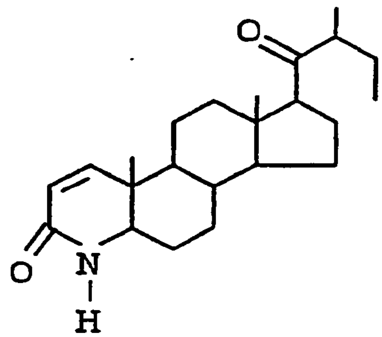
A suspension of 25.0 g of the above product from Example 1 was saponified with 12.5 g of KOH in 150.0 ml of 5:1 $CH_3OH$-$H_2O$ under reflux conditions for 4 hours/$N_2$. The mixture was cooled to 25°C and acidified to pH <2. Water (175 ml) was added gradually with stirring to leave a crystalline precipitate which was collected and washed with water.

After drying, the product amounted to 25 g., m.pt 313-315°C with decomposition.

The crude dry acid (23.0 g) was suspended in 210 ml of toluene, and to the suspension was added triphenylphosphine (56.0 g) and 2,2'-dipyridyl disulfide (48.3g), and the mixture was stirred at 24°C overnight/$N_2$. The reaction mixture was placed on a column of silica gel (1.3 kg) and was eluted with 1:1 (acetone/$CH_2Cl_2$). The desired thioester eluted slowly, and after rinsing with ether, yielded 36.8 g of the above-titled product, m.p. 232-235°C.

EXAMPLE 3

22-Methyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione



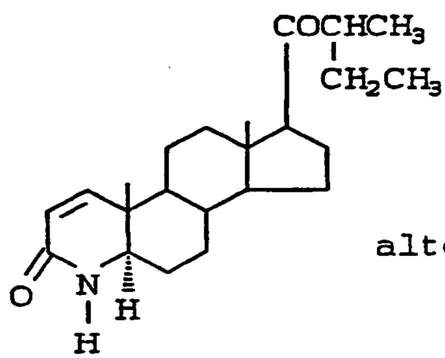
To a solution of 7.2 g of S-(2-pyridyl)-3-oxo-4-aza-5α-androst-1-ene-17β-thiocarboxylate in 288 ml of tetrahydrofuran was added at -78°C 33.6 ml of 1.3M S-butylmagnesium chloride. After 30 minutes at -78°C the solution came to room temperature and was treated with saturated aqueous NaCl solution. The product was extracted into dichloromethane and was washed with saturated aqueous NaCl solution and 10% aqueous NaOH solution, then dried and concentrated. The residue was eluted through 430 g of silica gel with 9:1 dichloromethane-acetone to give 4.5 g of the product, m.p. 246-249°C.

When the procedure is repeated using the following reagents, the indicated product is obtained.

| Starting Material | Reagent | Product |
|---|---|---|
| S-(2-pyridyl)3-oxo-4-aza-5α-androst-1-ene-17ß-thiocarboxylate | 2-pyrrolyl magnesium chloride | 17ß-(2-pyrrolyl-carbonyl)-4-aza-5α-androst-1-ene-3-one m.p. 294-296°C |
| S-(2-pyridyl)3-oxo-4-methyl-5α-androst-1-ene-17ß-thiocarboxylate | sec-butyl magnesium chloride | 4,22-dimethyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione m.p. 134-136°C |
| S-(2-pyridyl)3-oxo-4-methyl-4-aza-5α-androst-1-ene-17ß-thio-carboxylate | 2-pyrrolyl magnesium chloride | 4-methyl-17ß-(2-pyrrolylcarbonyl)-4-aza-5α-androst-1-ene-3-one m.p. 234-238°C |
| S-(2-pyridyl)3-oxo-4-aza-5α-androst-ene-17ß-thiocarboxylate | isobutyl magnesium chloride | 23-methyl-4-aza-21-nor-5α-cholane-3,20-dione m.p. 220-222°C |

EXAMPLE 4

22-Methyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione




alternate route

A solution of 21 g of 22-methyl-4-aza-21-nor-5α-cholane-3,20-dione and 29.49 g of benzeneseleninic anhydride in 552 ml of chlorobenzene was refluxed with water separation for 4 hours. The mixture was concentrated and the residue was redissolved in dichloromethane. After washing with 10% aqueous sodium hydroxide, then 10% hydrochloric acid and saturated aqueous sodium chloride the solution was dried and concentrated to 45 g of yellow residue. This was chromatographed on 1.5 kg of silica gel packed in dichloromethane and eluted with ethyl acetate to give 10.6 g of the product, m.p. 248-251°C.

When the procedure is repeated using 23-methyl-4-aza-21-nor-5α-cholane-3,20-dione as starting material the product obtained is 23-methyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione, m.p. 283-286°C.

## EXAMPLE 5

17ß-(phenylcarbonyl)-4-aza-5α-androst-1-ene-3-one

To a stirred suspension of 43 g of S-(2-pyridyl)-3-oxo-4-aza-5-alpha-androst-1-ene-17-beta-thiocarboxylate in 500 ml of anhydrous tetrahydrofuran (THF) was added at -78°C a THF solution of 157 ml of 2N phenylmagnesium chloride over 60 minutes. After stirring at -78°C for 60 minutes, the mixture was brought to -30°C and was quenched by addition of 10% HCl while maintaining the temperature below -20°C. After warming to 0°C, the mixture was diluted with 2000 ml of water and extracted with 4000 ml of dichloromethane in portions. The organic layer was washed sequentially with water, 1N sodium hydroxide, water and saturated sodium chloride solution. Drying with MgSO4 and concentration afforded 37.5 g of crude product. Recrystallization from dichloromethane/ ethyl acetate gave the title phenyl ketone (30.4 g, 77% yield).
m.p. 290-291°C.

| | Calc | Found |
|---|---|---|
| N | 3.61 | 3.56 |
| C | 77.48 | 77.16 |
| H | 8.26 | 8.19 |

## EXAMPLE 6

17-beta-4-fluorophenycarbonyl-4-aza-5-alpha-androst-1-ene-3-one

The procedure of Example 5 was repeated except using p-fluorophenylmagnesium bromide as the Grignard reagent and the title compound was obtained. m.p. 315-315.5°C.

EXAMPLE 7

17β-(cyclohexylcarbonyl)-4-aza-5α-androst-1-ene-3-one

To a suspension of 34.8 g of the thiopyridyl ester of Example 2 in 700 ml of anhydrous THF was added at -65 degrees C 130 ml of a 2 M ether solution of cyclohexyl magnesium chloride over a period of 20 minutes. After stirring at -70 degrees C for 60 minutes the solution was warmed and stirred at -10 degrees C for 60 minutes. The mixture was diluted with 500 ml of dichloromethane and then dropwise with dichloromethane, the phases were separated and the organic layer was treated sequentially with water, 1 N sodium hydroxide, water and saturated sodium chloride solution. The organic solution was decolorized with charcoal, filtered and concentrated to a residue which was crystallized from ethyl acetate to give 28.2 of the title compound, m.p. 271.5-277 degrees C.

EXAMPLE 8

The title compound of Example 7 was also prepared by the following procedure.

To a mixture of 150 g of methyl 3-oxo-4-aza-5-alpha-androst-1-ene-17-beta-carboxylate in 2800 ml of anhydrous THF was added with stirring at less than 0 degrees C internal temperature 678 ml of a 2 N ether solution of cyclohexyl magnesium chloride. The solution was then refluxed for 6 hours. The cooled (less than 10 degrees C) reaction

mixture was acidified with 10% HCl solution and was extracted with dichloromethane. The organic layer was washed sequentially with water, saturated NaHCO3 solution and saturated NaCl solution. Drying (MgSO4) and evaporation left 163 g of crude cyclohexyl ketone. Recrystallization from dichloromethane/ ethylacetate gave 131 g of the pure material.

m.p. 269-270 degrees C.

| | % Calc. | Found |
|---|---|---|
| N | 3.61 | 3.61 |
| C | 77.37 | 77.37 |
| H | 9.74 | 10.13 |

## EXAMPLE 9

**17-beta-(cyclopentylcarbonyl)-4-aza-5-alpha-androst-1-ene-3-one**

When the procedure of Example 7 or 8 was repeated using cyclopentylmagnesium chloride, the title compound was obtained:

m.p. 272-273 degrees C.

| | Calc | Found |
|---|---|---|
| N | 3.66 | 3.78 |
| C | 75.25 | 74.89 |
| H | 9.60 | 9.54 |

## EXAMPLE 10

17-beta-(cyclobutylcarbonyl)-4-aza-5-alpha-androst-1-ene-3-one

When the procedure of Example 7 or 8 was repeated using cyclobutylmagnesium chloride, the title compound was obtained:

m.p. 288-289 degrees C.

| | %Calc | Found |
|---|---|---|
| N | 3.94 | 3.87 |
| C | 77.71 | 78.06 |
| H | 9.36 | 9.61 |

## EXAMPLE 11

Synthesis of 17-ß-(4-Phenylbenzoyl)-4-aza-5a-androst-1-en-3-one

To a suspension of 258.0 mg of dry activated magnesium chips in 5.0 ml of dry THF was added 932.0 mg of 4-bromobiphenyl in 5.0 ml of dry THF under $N_2$. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 30 ml of 1,2-dibromoethane/$N_2$. The reaction was allowed to proceed for 1-1 1/2 hours at 28°C/$N_2$. The concentration of the Grignard reagent was 4.0 mmoles in 10.0 ml of dry THF.

The steroid from Example 2 (205.0 mg, 0.5mmol of thiopyridyl ester) was suspended in 2.0 ml of dry THF, cooled to -80°C and the above Grignard 3.80 ml was added via syringe to the steroidal

suspension over 5-10 minutes/$N_2$. The reaction was allowed to proceed for 1 hour at -80°C/$N_2$ and then at -10°C for an additional hour/$N_2$. The solution was diluted with 10.0 ml of methylene chloride and quenched with saturated aqueous solution of $NH_4Cl$ to pH=4. The organic layers were separated, washed 3 times with water, 3 times with saturated sodium chloride, dried over $MgSO_4$, filtered, and evaporated under vacuum to afford 156.2 mg of crude product. Crystallization from EtOAc gave the above-titled product in 98.58 mg, m.pt. 290°C-290.5°C.

Anald. Calcd. for $C_{31}H_{35}NO_2$:
C,82.08; H,7.78; N,3.09;
Found: C,81.84; H,8.01; N,3.06.
FAB: Calc. for $C_{31}H_{35}NO_2$: 453; Found: 453.

## EXAMPLE 12

17-ß-(3-Phenylbenzoyl)-4-aza-5a-androst-1-en-3-one

To a suspension of 258.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 932.0 mg of 3-bromobiphenyl in 2.0 ml of dry THF under $N_2$. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 30 microliters of 1,2-dibromoethane/$N_2$. The concentration of the Grignard reagent was 4 mmoles in 10.0 ml of dry THF.

The steroid from Example 2, 205.0 mg (0.5 mmoles) was suspended in 2.0 ml of dry THF, cooled to -80°C and the above prepared Grignard, 3.80 ml, was added via syringe to the steroidal suspension over

5-10 minutes/$N_2$. The reaction was allowed to proceed for 1 hour at -80°C/$N_2$ and then at -10°C for an additional hour/$N_2$. The solution was diluted with 10.0 ml of methylene chloride and quenched with a saturated aqueous solution of $NH_4Cl$ to pH=4. The organic layers were separated, washed 3 times with water, 3 times with saturated sodium chloride, dried over $MgSO_4$, filtered, and evaporated under vacuum. Crystallization from ethyl acetate afforded 122.84 mg of product. The material was purified on 20.0 g of silica gel column using 70:30 ($CHCl_3$-acetone) as eluant, to give a single spot material 117.0 mg of the above-titled compound, m.pt. 184-185°C.

Anald. Calcd. for $C_{31}H_{35}NO_2$:
C,82.08; H,7.78; N,3.09;
Found: C,82.28; H,8.04; N,2.98.
FAB: Calcd. for $C_{31}H_{35}NO_2$: 453; Found: 453.

## EXAMPLE 13

Synthesis of 17-ß-(4-Methylthiobenzoyl)-4-aza-5-α-androst-1-en-3-one

To a suspension of 250.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 812.0 mg of p-bromophenyl methyl sulfide in 3.0 ml of dry THF under $N_2$. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 40 µl of 1,2-dibromoethane/$N_2$. The reaction was allowed to proceed for 1 to 1 1/2 hours at 28°C/$N_2$. The concentration of the Grignard reagent was 4.0 mmoles in 10 ml of dry THF.

The steroid from Example 2, i.e. the pyridylthio ester, 205 mg, was suspended in 2.0 ml of dry THF, cooled to -80°C and the above prepared Grignard was added via syringe to the steroidal suspension in 5-10 minutes/$N_2$. The reaction was allowed to proceed for 1 hour at -80°C/$N_2$ and then at -10°C for an additional hour/$N_2$. The solution was diluted with 10.0 ml of methylene chloride, and quenched with saturated aqueous solution of $NH_4Cl$ to pH=4. The organic layers were separated, washed 3 times with water; 3 times with saturated sodium chloride, dried over $MgSO_4$, filtered, and evaporated under vacuum to afford 105.0 mg of crude product.

The crude product was chromatographed on TLC (one plate, 20 cm x 20 cm x 20 cm x 1000 μm silica gel) eluted with 80:20 ($CH_2Cl_2$-acetone) to afford 66.0 mg of single spot material. Crystallization from EtOAc afforded 45.0 mg of the above-titled compound, m.pt. 286-287°C.

FAB for $C_{26}H_{33}NO_2S$ (Calcd.) 424; Found 424.

## EXAMPLE 14

**Synthesis of 17-ß-(4-methylsulfinylbenzoyl) and -(4-methylsulfonylbenzoyl)-4-aza-5α-androst-1-en-3-one**

A. Oxidation

19.91 mg of the methylthio product from Example 13 was dissolved in 2.5 ml of $CH_2Cl_2$, cooled to 0-(-2)°C and was treated with a solution 9.6 mg of m-chloroperbenzoic acid in 1.0 ml of $CH_2Cl_2$ over a period of 4 minutes. After stirring for 1 hour at 0-(-2)°C, the reaction was diluted with 10 ml. $CH_2Cl_2$. The layers were washed subsequently with

2.5% $NaHCO_3$, $H_2O$ and saturated NaCl solutions. The organic layer was dried over $MgSO_4$ overnight, filtered and evaporated in vacuo to yield 17 mg product. Crystallization from EtOAc gave 11.8 mg of the above-titled compound, a solid, mp. 313-313.5°C (with dec.).

Anal. Calcd. for $C_{26}H_{33}NO_3S \cdot 1/4H_2O$:
C,70.31; H,7.60; N,3.15;
Found: C,70.47; H,7.70; N,3.00.

FAB for $C_{26}H_{33}NO_3S$ (Calcd. 440); Found 440.

Sulfone

Fifteen percent (15%) of the corresponding sulfone, 17ß-(4-methylsulfonyl benzoyl) derivative, was isolated by chromatography from the reaction as a byproduct. Recrystallized from EtOAc to yield a solid, mp. 279-279.5°C. Molecular weight by FAB showed 456; calculated 456.

Anal. for $C_{26}H_{33}NO_4S \cdot 0.25\ H_2O$
Calc: C,67.87; H,7.28; N,3.04.
Found: C,67.96; H,6.72; N,2.95.

EXAMPLE 15

Synthesis of 17-ß-(4-acetoxymethylthiobenzoyl)-4-aza-5α-androst-1-en-3-one

Trifluoroacetic anhydride (165 µl) was dissolved in 780 µl of acetic anhydride and kept for 5 hours at room temperature (RT).

To 300 µl of the above solution of mixed anhydrides was added 34.15 mg pure sulfoxide from Example 14 with stirring. A few minutes later 54.0 µl of 2,6-lutidine was added and the reaction was allowed to stir at $RT/N_2$ for 17 hours.

The liquid anhydrides were removed under reduced pressure and the remaining residue extracted (4 times with $CHCl_3$). The $CHCl_3$ extracts were washed subsequently with dilute HCl; 5% $NaHCO_3$ solution, 3 times; 3 times with $H_2O$; and finally with saturated NaCl solution, and then dried over $MgSO_4$ filtered and evaporated the solution to dryness _in vacuo_ to yield 42.1 mg of crude product.

The crude product from Step A was purified by chromatography on silica gel using 95:5 ($CHCl_3$-acetone) as eluant and then crystallizing the obtained solid from EtOAc to yield 17.8 mg of the above-titled compound as crystals, m.pt. 235-236°C (dec.).

Anal. Calcd. for $C_{28}H_{35}O_4NS \cdot 1/4\ H_2O$:
C,68.57; H,7.40; N,2.86;
Found: C,69.02; H,7.39; N,2.73.
FAB for $C_{28}H_{28}O_4NS$ calcd.: 482; Found 482.
The NMR (proton) was in agreement with the assigned product structure.

## EXAMPLE 16

Synthesis of 17ß(4-mercaptobenzoyl)-4-aza-5α-androst-1-en-3 one

40.0 mg of the acetoxy-methyl-thio derivative from Example 15 was suspended in 3.0 ml of isopropanol. The reaction mixture was flushed several times with $N_2$, and with vacuum, and the system kept under nitrogen atmosphere. To the above mixture was added 40.0 mg of $K_2CO_3$ in 2.00 ml of water (free of oxygen) via syringe, and the temperature of the reaction mixture was allowed to

rise to 80°C under gentle reflux under slight vacuum for 10 minutes, and then under $N_2$ for 1 hour. After 1 hour, the reaction mixture was a clear yellow solution. It was brought to R.T., cooled to 0-5°C and quenched with 2.5 N HCl acid/$N_2$. The reaction mixture was extracted 4 times with $CH_2Cl_2$. The organic layer was washed with $H_2O$ 4 times; 3 times with saturated salt solution, and finally dried over $MgSO_4$. Filtered and evaporated to dryness in vacuo to yield 36.9 mg of crude product. The crude product was dissolved in 2.0 ml of $CHCl_3$, filtered through Teflon (Acrodisc CR) and purified by preparative HPLC on silica gel and eluted with 60:40 ($CH_2Cl_2$-acetone). Crystallization, from EtOAc afforded a single spot material, 20.7 mg of the above-titled compound, m.pt. 285-286°C.

Anal. Calcd. for $C_{25}H_{31}O_2NS$ . 1/2 $H_2O$:
C,72.19; H,7.69; N,3.24;
Found: C,71.82; H,7.43; N,3.26.
FAB: Calcd. for $C_{25}H_{31}O_2NS$: 410; Found: 410.

## EXAMPLE 17

Synthesis of 17-ß-(4-Dimethylaminobenzoyl)-4-aza-5-a-androst-1-en-3-one

To a suspension of 291.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 800.0 mg of 4-bromo-N,N-dimethylaniline in 2.0 ml of dry THF under $N_2$. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 30 ml of

1,2-dibromoethane/$N_2$. The reaction was allowed to proceed for 1 to 1 1/2 hours at 28°C/$N_2$. The concentration of the Grignard reagent was 4.0 mmoles in 10.0 ml of dry THF.

The steroid from Example 2 (205 mg of pyridyl thioester) was suspended in 2.0 ml of dry THF, cooled to -80°C and the above Grignard 3.8 ml (3 equivalents) was added via syringe to the steroidal suspension over 5-10 minutes/$N_2$. The reaction was allowed to proceed for 1 hour at -80°C/$N_2$ and then at -10°C for an additional hour/$N_2$. The solution was diluted with 10.0 ml of methylene chloride and quenched with a saturated aqueous solution of $NH_4Cl$ to pH=4. The organic layers were separated, washed 3 times with water 3 times with saturated sodium chloride, dried over $MgSO_4$, filtered, and evaporated under vacuum to afford 151.3 mg of crude product. Crystallization from ethyl acetate gave 124.5 mg of the above-titled compound, m.pt. 268.5-269°C.

FAB: Calcd. $C_{27}H_{36}N_2O_2$: 421; Found: 421.

The NMR (proton in $CDCl_3$) confirmed the assigned structure.

EXAMPLE 18

General Procedure for Preparing Protected Silyl Derivatives

1.0 mole of phenol or its derivatives, or 1 mole of alcohol is treated with 1.5 liters of dry methylene chloride. To the clear solution is added dry 3.0 moles of imidazole/$N_2$. The clear solution is cooled to 0°C/$N_2$, and 2.0 moles of t-butyl dimethyl chlorosilane in 300.0 ml of dry methylene chloride is added dropwise at 0°C/$N_2$. Towards the end of the addition, precipitation occurs. The ice bath is removed, and the reaction is allowed to proceed overnight at R.T./$N_2$. Filter, wash the cake with cold $CH_2Cl_2$ solution, and the solvent is evaporated in vacuo to afford crude product. The crude product was readily purified by filtering through a silica gel column. (1 gr. of crude product per 100 g of silica gel, using $CH_2Cl_2$ as eluant) This method gives about 99% of pure silyl derivatives of phenols and alcohols.

EXAMPLE 19

Synthesis of 17-ß-(4-Hydroxybenzoyl)-4-aza-5-α-androst-1-ene-3-one

A. Grignard Reaction

To a suspension of 1.22 g of dry activated magnesium chips in 20.0 ml of dry THF was added 5.6 g of 1-bromo-4-(tertiary-butyl dimethyl silyloxy)benzene (prepared from p-bromophenol by the General Procedure detailed above) in 10.0 ml of THF under $N_2$. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 150 µl-200 µl of

1,2-dibromoethane/$N_2$. The reaction was allowed to proceed for 1-1 1/2 hours at 28°C/$N_2$. The concentration of the Grignard reagent formed was 19.5 mmoles in 30.0 ml of dry THF.

The steroid from Example 2 (1.02 g, 2.49 mmoles) was suspended in 20.0 ml of dry THF, cooled to -80°C and the above-prepared Grignard (11.5 ml) was added via syringe to the steroidal suspension in 5-10 minutes/$N_2$. The reaction was allowed to proceed for 1 hour at -80°C/$N_2$, and then at -10°C for an additional hour/$N_2$. The reaction solution was diluted with 10.0 ml of methylene chloride and quenched with a saturated aqueous solution of $NH_4Cl$ to pH=4. Organic layers were separated, washed 3 times with $H_2O$, 3 times with saturated sodium chloride, dried over $MgSO_4$, filtered, and evaporated under a vacuum to a yellow color solid. Crystallization from ethyl acetate afforded 607 mg of product m.p. 248-249°C.

Anal. Calcd. for $C_{31}H_{45}O_3NSi$:
C,73.32; H,8.93; N,2.75
Found: C,73.27; H,8.99; N,2.75.
FAB: Found 508; Calc. 508.

B. Desilylation

Dissolved 1.3g of product from above step A in 20.0 ml of dry THF. Cooled to -5°C and added 437 µl of glacial acetic acid/$N_2$. To the cold solution at -5°C was added via syringe 3.0 ml tetra-n-butylammonium fluoride dropwise under $N_2$ atmosphere. Allowed the reaction to proceed under stirring for 1

1/2-2 hours at 0° to -5°C/$N_2$. The reaction mixture was poured into a 2-layer mixture of ethyl acetate/sodium bicarbonate saturated solution at 0°C. The water layer was separated and further extracted with EtOAc 3 times and with $CH_2Cl_2$ (3 times).

The organic layers were combined, washed 3 times with $H_2O$, 1 time with saturated sodium chloride solution, and dried over $MgSO_4$, filtered and evaporated to dryness under vacuum. The crude product was crystallized from ethyl acetate to afford 977.9 mg, and further recrystallized from methanol to afford 842.3 mg of the above-titled product, m.pt. 296-297°C.

Anal. Calcd. for $C_{25}H_{31}NO_3 \cdot 1/3\ H_2O$:
C,75.15; H,7.98; N,3.51.
Found: C,75.13; H,7.76; N,3.54.
(Mass Spec.) FAB: Found 394; Calcd. 394.

## EXAMPLE 20

**17-ß-(3,5-dimethyl-4-hydroxybenzoyl)-4-aza-5α-androst-1-ene-3-one**

A. Preparation of Grignard Reagent

To a suspension of 260.0 mg of dry activated magnesium chips in 6.0 ml of dry THF was added 628.0 mg of 1-bromo-3,5-dimethyl-4-tertiary-butyl-dimethyl-silyloxybenzene (prepared from 4-bromo-2,6-dimethylphenol by the General Procedure described above) in 4.0 ml of $THF/N_2$. The reaction was conducted in an ultrasonic bath at a temperature

range of 24°-30°C. To the well-agitated mixture was added dropwise 40 µl of 1,2-dibromoethane/$N_2$. The reaction was allowed to proceed for 2 hours/$N_2$. The concentration of the Grignard reagent thus formed was 2 mmoles in 10.0 ml of dry THF.

The steroid from Example 2 (205.0 mg (0.5 mmoles) was suspended in 3.0 ml of dry THF, cooled to -80°C, and 7.5 ml (1.50 millieq.) of the above-prepared Grignard was introduced via syringe to the steroidal suspension over a period of 5-10 minutes/$N_2$. The reaction was allowed to proceed for 1 hour at -80°C/$N_2$ and then at -10°C for additional hour/$N_2$.

The reaction was quenched with 1N HCl, and then diluted with chloroform. The organic layers were combined, washed 3 times with $H_2O$, 3 times with saturated sodium chloride and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was washed with ether to afford 121.7 mg of product.

The crude product was dissolved in 70:30 ($CHCl_3$-acetone), filtered through Teflon (Acrodisc CR) and purified by preparative HPLC (Waters Prep-pak) on silica gel and eluted with 70:30 ($CHCl_3$-acetone).

The major component was recrystallized from ethyl acetate to give 52.0 mg of product m.pt 245-245.5°C.

Anal. Calcd. for $C_{33}H_{49}O_3NSi$:
C,73.96; H,9.23; N,2.61
Found: C,74.06; H,9.33: N,2.64
(Mass Spec.) FAB: Found: 536; Calc.: 536

B. Deblocking the Silyl Derivative

Dissolved 54.0 mg of the above product from A in dry THF (1.3 ml). The clear solution was cooled to 0°C, and 29 µl of glacial HOAc was added via syringe/$N_2$. To the above solution was added dropwise 172 µl of tetra-n-butylammonium fluoride at 0°C dropwise via syringe/$N_2$. Allowed the reaction to proceed at 0°C/$N_2$ for 1 1/2 hours. The reaction mixture was poured into ice/saturated $NaHCO_3$ solution and EtOAc. Stirred for several minutes. Allow the layers to separate, and the $H_2O$ layer was extracted 3 times with EtOAc and 3 times with $CHCl_3$.

Combined the organic layers and washed 3 times with $H_2O$, then 3 times with saturated NaCl, and then dried over $MgSO_4$, filtered and evaporated to dryness in vacuum to afford 52.2 mg.

The product was crystallized from EtOAc to give 22.5 mg of the above-titled product m.pt 305-306°C.

Calc. for $C_{27}H_{35}O_3N \cdot H_2O$:
C, 73.77; H, 8.49; N, 3.10.
Found: C, 73.62; H, 7.90; N, 3.44.
(Mass Spec.) FAB: Calc:422; Found: 422

EXAMPLE 21

Synthesis of 17-ß-(4-Methoxybenzoyl)-4-aza-5-α-androst-1-ene-3-one

A. Grignard Reaction

To a suspension of 258.0 mg of dry activated Mg chips in 8.0 ml of THF/$N_2$ was added 748.0 mg p-bromoanisole in 2.0 ml of dry THF. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C/$N_2$. To the well-agitated mixture was

added dropwise 30.0 µl of 1,2-dibromoethane as a catalyst. The reaction was allowed to progress for 1-2 hours at 28°C. The formed Grignard reagent had a concentration of 4 mmoles in 10.0 µl of dry THF.

The steroid from Example 2 (205.0 mg (0.50 mml) was suspended in 2.0 ml of THF, cooled to -78°C and the above-prepared Grignard reagent (3.75 ml; 14 milliequivalents) was added via syringe to the steroidal suspension over 5-10 minutes/$N_2$ and then at -10°C for an additional hour/$N_2$. The resulting reaction mixture was a clear solution, which was cooled to 0-5°C, diluted with chloroform and quenched with 1N HCl acid. The organic layers were separated, washed with $H_2O$ 2 times, followed with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was washed with ether, and crystallized from EtOAc to give 110 mg of product m.pt 305-306°C.

Further purification was carried out by chromatographic isolation on a TLC. plate, (20 cm x 20 cm x 1000 µm), using as eluant, 70:30 ($CHCl_3$: acetone). Recrystallization from EtOAc yielded 78.56 mg of the above-titled product, m.pt 305-306°C (dec.).

(Mass Spec) FAB: Calcd.,408; Found 408.

## EXAMPLE 22

Synthesis of 17-ß-(3-hydroxybenzoyl)-4-aza-5α-androst-1-ene-3 one

A. Preparation of Grignard Reagent

To a suspension of 230.0 mg of dry activated Mg chips in 2.0 ml of dry THF was added 722.4 mg of

1-bromo-3-tertiary-butyl dimethyl-silyloxybenzene (prepared from 3-bromophenol by the General Procedure described above) in 8.0 ml of dry THF/$N_2$. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C/$N_2$. To the well-agitated mixture was added dropwise 20.0 µl of 1,2-dibromoethane/$N_2$. Allowed the reaction to progress for 2 1/2 hours at 28°C/$N_2$. The formed Grignard reagent had a concentration of 2.52 mmoles in 10.0 ml of dry THF.

The steroid from Example 2 (205.0 mg (0.5 mmoles) was suspended in 2.0 ml of THF, cooled to -78°C and the above-prepared Grignard reagent (6.0 ml, (1.5 milliequivalents) was added via syringe to the steroidal suspension over 5-10 minutes/$N_2$, and then stirred for an additional hour at -10°C/$N_2$. The clear reaction mixture was quenched at 0 to -5°C with 1N HCl acid for 10.0 minutes and diluted with $CHCl_3$. The combined organic layers were washed 3 times with $H_2O$, 3 times with saturated NaCl, and then dried over $MgSO_4$, filtered and concentrated in vacuo to afford crude product. The product was purified on silica gel column and was eluted with 70:30 ($CHCl_3$-acetone). The desired product amounted to 58.0 mg, as the silyl derivative, 17ß-(3-tertiary-butyl-dimethylsilyloxybenzoyl)-4-methyl-4-aza-5α-androst-1-en-3-one.

B. Deblocking

57.6 mg of the above silyl derivative was dissolved in 3.0 ml of dry THF. The solution was cooled to 0°C, and 20 µl of glacial acetic acid was

introduced via syringe. To the clear solution was added 130.0 µl of (n-butyl)$_4$NF via syringe, and allowed the reaction to proceed for 1 hour/$N_2$ at 0°C. The reaction mixture was poured into EtOAc/$NaHCO_3$ sat. solution @ 0°C. The water layer was separated, extracted 3 times with EtOAc and then 3 times with chloroform. The organic layers were combined and washed 3 times with $H_2O$, 3 times with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated in vacuo to give 57.11 mg of crude product. The crude product was chromatographed by TLC (one plate, 20 cm x 20 cm x 250 µm silica gel), eluted with 70:30 ($CHCl_3$-acetone) to afford 44.5 mg of the above-titled product. Recrystallization from EtOAc gave 29.30 mg m.pt 279-280°C.

Anal. Calcl. for $C_{25}H_{31}NO_3$: $8H_2O$:
C,73.60; H,8.06; N,3.43.
Found: C,73.26; H,8.22; N,3.28.
(Mass Spec.) FAB: Calcd: 394; Found 394.

## EXAMPLE 23

Synthesis of 17-ß-(4-hydroxymethyl-benzoyl)-4-aza-5α-androst-1-en-3-one

A. Preparation of Grignard solution

To a suspension of 100.0 mg (4 mmoles) of dry activated Mg chips in 5.0 ml of dry THF/$N_2$, was added 753.0 mg (2.5 mmoles) of 1-bromo-4-tertiary-butyl dimethyl silyloxy methyl benzene (prepared from 4-bromobenzyl alcohol by the General Procedure described above). The reaction was conducted in an ultrasonic bath at a temperature range of 24-30°C/$N_2$. To the well-agitated mixture was

added 20 µl of 1,2-dibromoethane/$N_2$. Allowed the reaction to progress for 2 hours at 28°C/$N_2$. The concentration of formed Grignard was 2.5 mmoles in 5.0 ml of dry THF.

B. Grignard Reaction

The steroid from Example 2 (205.0 mg (0.5 mmoles) was suspended in 2.0 ml of THF, cooled to -78°C, and the above-prepared Grignard (3.0 ml, 3.75 milliequivalents) was introduced via syringe into the steroidal suspension over 5-10 minutes/$N_2$. Allowed the reaction to progress for 1 hour at -80°C/$N_2$, and then for an additional hour at -10°C/$N_2$. The clear reaction solution was quenched with saturated $NH_4Cl$ at 0° to -5°C, and then diluted with $CH_2Cl_2$. The organic layers were separated and washed 3 times with water, 3 times with saturated NaCl, dried over $MgSO_4$, filtered and evaporated in vacuo to dryness. Crude product was crystallized from EtOAc to give 137.8 mg of silyl product.

(Mass Spec.) FAB: Calcd for $C_{30}H_{41}O_3NSi$: 521.75
Found: 522.0.

C. Deblocking of Silyl Derivative

The product from Step B above (23.67 mg) was dissolved in 0.5 ml of THF and 0.5 ml of MeOH and cooled to 0°C/$N_2$. To the cold solution was added 10 µl of concentrated sulfuric acid (98%). The reaction was stirred for 45 minutes at 0°C/$N_2$. To the cold solution at 0°C was slowly added a saturated solution of $NaHCO_3$ and chloroform. Extracted 3 times with $CHCl_3$. The organic layers were washed 3 times with water, 3 times with saturated NaCl, solution dri d

over $MgSO_4$, filtered and evaporated to dryness in vacuo, to afford 10.18 mg. After chromatography on a TLC plate (elution with 1:1 $CHCl_2$: acetone) The crude product was crystallized from EtOAc to give 6.0 mg of the above-titled product, m.pt 318-320°C.

Anal. Calcd. for $C_{26}H_{33}O_3N.1/3H_2O$:
C,75.41: H,7.94; N,3.38.
Found: C,75.61; H,7.84; N,3.12.
(Mass Spec.) FAB: Calc.: 408; Found: 408

## EXAMPLE 24

Synthesis of 17-ß-(4-Carboxybenzoyl)-4-aza-5α-androst-1-en-3-one

A. Oxidation

90.2 mg of the product from Example 23 was dissolved in 2.63 ml of glacial acetic acid and to the clear solution was added 69.0 mg of $CrO_3$ (previously dried over $P_2O_5$ at R.T. for 2 days in vacuo). After stirring overnight, the reaction mixture was diluted with water and allowed to age overnight in the refrigerator. The reaction mixture was filtered and the mother liquor and washes were extracted overnight using a liquid-liquid extractor, ($H_2O$-EtOAc) under reflux conditions. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was dissolved in hot MeOH, filtered and evaporated in vacuo to afford a product weighing 32.0 mg.

FAB: Calc. for $C_{26}H_{31}O_4N$: 422.0;
Found: 422.

B. Purification

The above free acid was purified by dissolving the above product in 1N sodium hydroxide solution. The clear solution was extracted 3 times with EtOAc. The aqueous basic solution was cooled and acidified with 1N HCl acid dropwise to pH=4 with stirring. The reaction mixture was allowed to age for 1 hour at 0°C. It was filtered and the residue was washed with cold water. Dried overnight to 100°C in vacuum <0.2 mm pressure.

Yield of the above-titled free acid was 9.85 mg.
FAB: Calc. for $C_{25}H_{31}O_4N$: 422; Found 422.
NMR analysis indicated the product to be an acid.

C. Sodium Salt of Above Acid

4.9 mg of the above product acid B was dissolved in 2.0 ml of hot methanol. To the clear solution, was added 11.6 µl of 1N NaOH(aq). To solution after methanol evaporation in vacuo, was added water to reach pH 7.21. The aqueous solution was freeze dried to give 6.3 mg of the sodium salt of the above-titled product.

## EXAMPLE 25

Synthesis of 17-ß-(4-hydroxyethylbenzoyl)-4-aza-5α-androst-1-en-3-one

A. Grignard Reagent

To a suspension of 252 mg of dry activated Mg chips in 10.0 ml of dry THF was added 1.26 g (4 mmoles) of 1-bromo-4 tertiary-butyl dimethyl silyloxy ethyl benzene (prepared from 2-(p-bromophenyl) ethanol

by the General Procedure described above). The reaction mixture was vigorously stirred using an ultrasonic vibrator/$N_2$. To the well-agitated mixture was added 40 µl of 1,2-dibromoethane to catalyze the above reaction. Allowed the reaction to progress for 3 1/2-4 hours/$N_2$. The concentration of formed Grignard reagent was 4 mmoles in 10 ml of THF.

B. <u>Grignard Reaction</u>

205.0 mg (0.5 mmoles) of the aza-steroid of Example 2 was suspended in 2.0 ml of dry THF/$N_2$, cooled to -80°C, and the above-prepared Grignard (3.75 ml, 1.5 milliequivalents) via syringe was introduced into the steroidal suspension over 5-10 minutes/$N_2$. The reaction was run at -80°C for 1 hour/$N_2$ and then for an additional hour at -10°C. The reaction was quenched with a saturated solution of $NH_4Cl$ at 0-5°C and diluted with 10.0 ml of $CH_2Cl_2$. The organic layers were washed with water (3 times), saturated NaCl solution (3 times), dried with $MgSO_4$, filtered and evaporated in vacuo to dryness. The crude product was crystallized from EtOAc overnight to give 152.0 mg of product m.pt. 233-234°C.

Anal. Calcd. for $C_{33}H_{49}O_3NSi$:1/4 $H_2O$:
C,73.55; H,9.18, N,2.59.
Found: C,73.45; H,8.94; N,3.21
FAB: Calc. 536; Found: 536

C. <u>Desilylation</u>

70.8 mg of product from Step B, was dissolved in 1.45 ml of methanol and 1.45 ml of THF. The solution was cooled to 0-5°C and 29 µl of conc.

$H_2SO_4$ was added via syringe under $N_2$. The reaction was allowed to proceed for 45 minutes/$N_2$. The reaction was carefully quenched at 0°C with a saturated solution of $NaHCO_3$, and extracted 3 times with $CH_2Cl_2$. The organic layers were separated, washed with water (3 times), then with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated in vacuo to give 43.0 mg of crude product. The crude product was placed on a column of silica gel and was eluted with 1:1 acetone-$CH_2Cl_2$. The isolated product was crystallized from anhydrous methanol to afford 20.0 mg of the above-titled product m.pt 292-293°C with dec.

Anal. Calcd. for $C_{27}H_{35}O_3N.1/4\ H_2$:
C,75.31; H,8.25; N,3.25.
Found: C,75.49; H,8.29; N,3.45.
FAB: Calcd 422; Found 422.

## EXAMPLE 26

Synthesis of 17-ß-(4-carboxymethylbenzoyl)-4-aza-5α-androst-1-en-3-one

A. Oxidation

13.0 mg of the product from Example 25 was dissolved in 1 ml of glacial acetic acid. To the clear solution was added 10.0 mg of $CrO_3$ (previously dried over $P_2O_5$ in vacuum at R.T.). Allowed the reaction to progress overnight at R.T., and then at 0°C for 48 hours. The addition of 7.0 ml of water caused the product to crystallize overnight in a refrigerator. The crude product was isolated, washed with cold water and dried in a vacuum at 110°C below 1 mm pressure.

The dried crude product was dissolved in IN sodium hydroxide and the basic solution was extracted 3 times with methylene chloride (The organic layers were separated, and the aqueous basic solution was cooled and acidified with 1.5 N hydrochloric acid. The precipitate was filtered, washed with water dried at 110°C under vacuum at 0.1 mm pressure.

Yield of above-titled product=7.0 mg.

FAB Calc. $C_{27}H_{33}O_4N$: 436; Found 436.

EXAMPLE 27

Synthesis of 17-ß-(3,4-dihydroxybenzoyl)-4-aza-5α-androst-1-en-3-one

A. Grignard

To a suspension of 258.5 mg of dry activated magnesium chips in 10.0 ml of dry THF, was added 482 mg. of 4-bromo-1,2-methylenedioxybenzene/$N_2$. (The starting material is commercially available from Aldrich Chemical) The reaction was conducted in an ultrasonic water bath at a temperature range of 24°-30°C. To the well-agitated mixture was added 40 µl of 1,2-dibromoethane as a catalyst/$N_2$, and the reaction was allowed to progress for 1 1/2-2 hours at 28°C/$N_2$. The concentration of the formed Grignard reagent was 3.75 mmoles in 10 ml of dry THF.

The steroid from Example 2 (410 mg, 1mmole) was suspended in 4.0 ml of dry THF/$N_2$ and cooled to -80°C and 8.0 ml of the above-prepared Grignard (3.04 milliequivalents) was added via syringe to the steroidal suspension/$N_2$ over a period of 5-10 minutes. The reaction was allowed to proceed for 1

hour at -80°C, and then at -10°C for an additional hour/$N_2$. The reaction mixture was diluted with $CH_2Cl_2$, and then quenched with 1N HCl at -5°C.

The organic layers were collected and washed with water 3 times, saturated NaCl solution 3 times, dried over $MgSO_4$, filtered and evaporated in vacuo to dryness. Purification of the crude product was carried out on 50.0 g of silica gel using as eluant 1:1($CH_2Cl_2$-acetone) to give 347.0 mg.

FAB showed 422; Calcd. 422.

62.4 mg of the above product was crystallized from EtOAc to afford 11.39 mg of product m.pt.324-325°C.

Anal. Calcd. for $C_{26}H_{31}O_4N$ .3/4 $H_2O$:
C,71.78; H,7.53; N,3.22.
Found: C,71.90; H,7.54; N,3.25.
FAB for $C_{26}H_{31}O_4N$ showed 422; Calcd: 422.

B. Cleavage of Methylene Dioxylan Group

70.0 mg of the product from Step A was dissolved in dry 25.0 ml of 1,2-dichloroethane at R.T./$N_2$. The solution was allowed to cool to -10°C, and 1.03 ml of $BBr_3$ (1.0 M solution in dichloromethane) was added dropwise under $N_2$ atmosphere. The reaction was allowed to proceed at R.T. for 3 1/2-4 hours/$N_2$. After 4 hours/$N_2$, the reaction was cooled to (-10°C) and quenched with 10.0 ml of methanol for 10 minutes at 0°C, and then gradually the temperature was allowed to rise to R.T./$N_2$. The reaction mixture was evaporated in vacuo to dryness. The residue was extracted 3 times with EtOAc. The organic layers were washed with

water 3 times, 2 times with saturated $NaHCO_3$ solution, 3 times with water and finally with a saturated solution of NaCl. The organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was chromatographed on 2 silica gel plates, (20 cm x 20 cm x 20 cm x 250 µm) eluted with 1:1 (acetone - methylene chloride). Recrystallization from EtOAc afforded 5.0 mg of the above-titled product m.p. 222-222.5°C.

Anal. Calcd. for $C_{25}H_{31}O_4N$ . 1/2 $H_2O$:
C,71.78; H,7.66; N,3.35.
Found: C,71.71; H,7.71; N,3.33.
FAB: Calcd. for $C_{25}H_{31}O_4N$: 410; Found 410.

## EXAMPLE 28

Synthesis of 17-ß-(2 methoxybenzoyl)-4-aza-5α-androst-1-ene-3-one

A. Grignard

To a suspension of 258.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 771.0 mg of o-bromoanisole in 2.0 ml of dry THF/$N_2$. The reaction was conducted in an ultrasonic water bath at a temperature range of 24-30°C. To the well-agitated mixture was added 30 µl of 1,2-dibromoethane/$N_2$, and the reaction was allowed to progress for 2 hours at 28°C/$N_2$. The concentration of the formed Grignard reagent was 4 mmoles in 10.0 ml of dry THF.

The steroid from Example 2 (205 mg, 0.5 mmoles) was suspended in 2.0 ml of dry THF/$N_2$, cooled to -79°C, and 4.0 ml of the above-prepared Grignard

(1.6 milli-equivalents) was added via syringe to the steroidal suspension/$N_2$ over a period of 5-10 minutes. The reaction mixture was allowed to proceed for 1 hour at -80°C, and then at 0-2°C for an additional hour/$N_2$. The reaction mixture was diluted with $CH_2Cl_2$ and then quenched with 1N HCl solution at 0°C.

The organic layers were combined, washed 3 times with water, 3 times with saturated NaCl solution; and dried over $MgSO_4$. Filtered and evaporated in vacuum to dryness. The crude material was crystallized from EtOAc to give 124.5 mg of product m.pt 228-230°C. Purification on silica gel column using 70:30 ($CHCl_3$-acetone) gave a single spot material in a yield of 83.0 mg m.pt. 241-241.5.

Anal. Calcd. for $C_{26}H_{33}O_3N$:
C,76.91; H,8.19; N,3.45
Found: C,76.36; H,8.26; N,3.35.
FAB calcd. for $C_{26}H_{33}O_3N$: 406; Found: 406.

B. Cleavage of Methoxy Group

12.7 mg (0.03 mmoles) of the product from Step A was dissolved in 5.0 ml of dry methylene chloride/$N_2$. To clear solution at -79°C/N, was added 50 µl of 1 mmole/ml of $BBr_3$ in $CH_2Cl_2$ via syringe dropwise. Allowed the reaction to proceed at R.T. overnight/$N_2$ with rapid stirring. Next day, a clear yellow solution was obtained. The reaction mixture was cooled to 0-2°C and quenched with water, to hydrolyze excess of $BBr_3$. The organic phase was washed 3 times with dilute sodium hydroxide, 3 times with water, 3 times with dilute HCl, 3 times with

water, 3 times with saturated NaCl solution, and dried the organic layer over $MgSO_4$. Filtered, concentrated in a vacuum to dryness. The crude product crystallized from EtOAc to afford 7.0 mg of a pure single spot material being 17-ß-(2-hydroxymethyl-benzoyl)-4-aza-5-α-androst-1-en-3-one.

FAB for $C_{25}H_{31}NO_2$; Calcd: 394; Found: 394.

## EXAMPLE 29

17ß(α-hydroxybenzyl)-4-aza-5α-androst-1-ene-3-one

570 milligrams of 17ß-benzoyl-4-aza-5α-androst-1-ene-3-one (prepared from the thiopyridyl ester of Example 2 and commercially available phenyl magnesium bromide, analogously via the procedure in Example 5, to produce the 17-benzoyl derivative, mp. 295-296°C crystallized from EtOAc) was suspended in 80 ml of anhydrous isopropanol. To the suspension was added 500.0 mg of $NaBH_4$ in 5 portions. When all the hydride was added, 20.0 ml of dry THF was carefully added, so that the reaction mixture became a clear solution. Allowed the reaction to proceed at R.T./$N_2$ overnight. The reaction was quenched carefully with 1N HCl, and allowed to stir under $N_2$ for an additional hour at R.T. It was then diluted with water, and extracted 3 times with $CHCl_3$. The organic layers were combined, washed 3 times with $H_2O$; 3 times with saturated NaCl solution, and dried over $MgSO_4$. Filtered and evaporated to a white solid weighing 495.0 mg.

The crude material was crystallized from EtOAc to afford 349.5 mg of material. Further purification on a silica gel column, using as eluant,

70:30 ($CHCl_3$-acetone) gave a single spot material, 221 mg, of the above-titled compound, m.pt 296-297°C.

Anal. Calcd. for $C_{25}H_{33}NO_2$:
C,79.17; H,8.78; N,3.70.
Found: C,79.24; H,8.85; N,3.48.
FAB Calcd. for $C_{25}H_{33}NO_2$: 380; Found: 380.

## EXAMPLE 30

17ß-hydroxymethyl-4aza-5α-androst-1-ene-3-one

500.0 mg of S-2-pyridyl-3-oxo-4-aza-5α-androst-1-ene-3 one (Example 2) was dissolved in 40.0 ml of dry THF at R.T./$N_2$. The solution was cooled to -78°C/$N_2$ and 5.5 ml of 1 M dibutyl aluminium hydride in THF was slowly added via syringe to the solution, with rapid stirring. Allowed the reaction to proceed at -76 to -78°C for half an hour under $N_2$. The temperature was gradually brought to R.T. and the reaction mixture kept for 2-1/2 hours/$N_2$. The reaction was then quenched at 0° to 5°C with 2N HCl acid, and then diluted with $CHCl_3$. The organic layers were separated, washed with $H_2O$ 3 times, then with saturated NaCl solution, and finally dried over $MgSO_2$. Filtered, and the organic phase was evaporated under vacuum to give 216.0 mg of crude product.

The crude product was chromatographed on 20.0 g of E.M. silica gel column, using 70:30($CHCl_3$-acetone) as eluant.

Yield of single spot material was 126.3 mg of the above-titled compound, m.pt. 271-271.5°C.

Calcd. for $C_{19}H_{29}O_2N$: FAB 304; Found 304.
NMR in $CDCl_3$ confirmed the above structure.

EXAMPLE 31

17ß-Formyl-4-aza-5α-androst-1-ene-3-one

Into a 100.0 ml dry flask was placed 1.3 ml of oxalyl chloride (2 M in $CH_2Cl_2$) with 50.0 ml of dry $CH_2Cl_2/N_2$. The above solution was cooled to -78°C and 338 µl of DMSO was added dropwise via syringe/$N_2$. The mixture was stirred at -78°C/$N_2$ for 30 minutes, and a solution of above-prepared alcohol from Example 15, i.e. 17ß hydroxymethyl-4-aza-5α-androst-1-ene-3-one (256.9 mg in 15.0 ml of dry $CH_2Cl_2/N_2$ was added via syringe. The reaction was allowed to progress for one hour at -78°C/$N_2$. After an hour at -78°C, was added 1 ml of dry triethylamine at a rapid rate. Reaction was raised slowly to R.T./$N_2$ with stirring, the resulting yellow solution was then poured into 50.0 ml of cold water. The organic layers were washed with a saturated solution of $NaHCO_3$, and then with a saturated solution of NaCl. Dried over $MgSO_4$, evaporated the solvent under vacuum to give 172.4 mg of crude product. The crude product was chromatographed on 60.0 g silica gel column using 70.30 ($CHCl_3$-acetone), to give a single spot material. Crystallization from EtOAc afforded the above-titled compound, 37.7 mg, m.pt. 258-259°C.

EXAMPLE 32

Synthesis of diastereoisomeric 17ß(α-hydroxybenzyl)-4-aza-5α-androst-1-ene-3-ones

26.3 of above-prepared formyl derivative (from Example 31) was dissolved in 7.0 ml of dry THF/$N_2$. The solution was cooled to -78°C/$N_2$, and 131

µl of phenyl magnesium bromide (Aldrich reagent) 0.393 milliequivalents) in dry THF was added dropwise via syringe/$N_2$. Allowed the reaction to proceed for 1 hour/$N_2$ at -78°C and then at R.T. for addition hour/$N_2$.

The reaction was quenched at 0-5°C with 2.5N HCl, and then diluted with $CHCl_3$. Organic layers were separated, washed 3 times with water; 3 times with saturated NaCl solution, dried over $MgSO_4$. Filtered and evaporated in vacuum to dryness to afford 28.6 mg of crude product. Analysis of the NMR spectra and peak heights from HPLC indicated this product to be a 1:1 mixture of diastereoisomers. The crude product was filtered through a 1 µm Teflon filter and purified by HPLC on a Whitman Portisil 10 column using 70:30($CHCl_3$-acetone). The FAB mass spectrum indicated the same $M^{+}$+1 for both isomers, being 380 mass units. The faster eluting isomer, m.pt. 289-289.5°C, was crystallized from EtOAc and showed a single spot material on TLC.

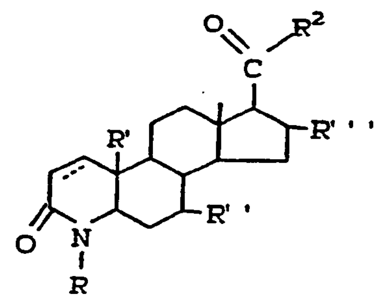
Anal. Calcd. for $C_{25}H_{33}NO_2 \cdot 1/4\ H_2O$;
C,78.39; H,8.81; N,3.65.
Found: C,78.11; H,8.65; N,3.58.

The slower eluting isomer, m.pt. 300-301°C showed a single spot material on TLC. The faster isomer showed by NMR($CDCl_3$): $CH_3$ at C-18 was deshielded (0.89δ) as compared to the slower isomer $CH_3$ at C-18 at (0.69δ). The benzilic proton for the faster isomer was also deshielded (4.5δ) versus (4.95δ). The olefinic proton at C-1 showed deshielding effects for the faster isomer at (6.81δ) to (6.62δ). From th above data, the two isomers showed distinctly different physical properties.

WHAT IS CLAIMED IS:

1. A method of treating humans for patterned alopecia, which comprises the concomitant administration of a therapeutically effective amount of:

(A) a compound of the formula:



wherein the dotted line represents a double bond when present and ,

R is selected from hydrogen, methyl and ethyl; and

$R^2$ is
(a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of $C_1$-$C_2$ alkyl or halo;
(b) an aralkyl radical selected from benzyl or phenethyl;
(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, -O$C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkyl, halo or nitro;
(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, $-OC_1-C_4$ alkyl, $C_1-C_4$ alkyl, $-(CH_2)_mOH$, $-(CH_2)_n$, COOH, including protected hydroxy, where m is 1-4, n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, $-SC_1-C_4$ alkyl, $-SOC_1-C_4$ alkyl, $-SO_2C_1-C_4$ alkyl, $-SO_2N(C_1-C_4\text{-alkyl})_2$, $C_1-C_4$ alkyl $-(CH_2)_mSH$, $-S-(CH_2)_n-O-COCH_3$, where m is 1-4 n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above sulfur containing radicals is present;

(3) $N(R^3)_2$, which can be protected, where $R^3$ is independently H or $C_1-C_4$ alkyl, where the monoaryl ring can also be further substituted with $C_1-C_4$ alkyl; and

(e) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;

R', R'', R''' are each selected from hydrogen and methyl, and pharmaceutically acceptable salts thereof, administered systemically, topically or orally, and

(B) minoxidil, administered topically.

2. The method of Claim 1

wherein the dotted line is a double bond,
R is hydrogen or methyl;
R'' and R''' are hydrogen; and
$R^2$ is phenyl, 2-, 3-, or 4-tolyl, xylyl, 2-bromophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 2,6-dibromophenyl, aminophenyl, N-alkylaminophenyl, N-N-dialkylaminophenyl, 4-biphenyl, 3-biphenyl, naphthyl, anthracyl, phenanthryl, thiophenyl, methylthiophenyl, methylsulfinyl, phenyl, methylsulfophenyl, aminosulfophenyl, thioethylphenyl, acetoxymethylthiophenyl, 17ß-(4-hydroxyphenyl),17ß-(3-hydroxyphenyl), 17ß-(3,4-dihydroxyphenyl), or 17ß-(3,5-dimethyl-4-hydroxyphenyl).

3. The method of Claim 2 in which the compound which is

17ß-(phenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17ß-(2-tolylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17ß-(3-tolylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;
17ß-(4-tolylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(2-bromophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(2-chlorophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(2,6-dichlorophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(2,6-dibromophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(xylylcarbonyl)-4-aza-4-methyl-5α-androst-1-ene-3-one;

17ß-(t-butylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(isobutylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(isooctylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(n-octylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(1,1-diethylbutylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(neopentylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(tert-amylcarbonyl)-4-aza-4-5α-androst-1-ene-3-one;

17ß-(tert-hexylcarbonyl)-4-aza-4-5α-androst-1-ene-3-one;

17ß-(cyclohexylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(cyclopentylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(benzylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-pyridylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(4-pyridylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-pyrrolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-furylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-thiophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-adamantylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(phenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-tolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(3-tolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(4-tolylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-bromophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2-chlorophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2,6-dichlorophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(2,6-dibromophenylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(xylylcarbonyl)-4-aza-5α-androst-1-ene-3-one;

17ß-(phenylethyl)carbonyl-4-aza-5α-androst-1-ene-3-one;

17ß-(4-dimethylaminophenylcarbonyl)-4-aza-5a-androst-1-en-3-one;

17ß-(3-dimethylaminophenylcarbonyl)-4-aza-5a-androst-1-en-3-one.

17ß-(3,4-diethylaminophenylcarbonyl)-4-aza-androst-1-en-3-one.

17ß-(3,5-dimethyl-4-diethylaminophenylcarbonyl)-4-aza-5a-androst-1-en-3-one;

17ß-(4-N-methylaminomethylphenylcarbonyl)-4-aza-5a-androst-1-en-3-one; or

17ß-(2-N-ethylamino-4-ethylphenylcarbonyl)-4-aza-5a-androst-1-en-3-one.

17ß-(4-phenylbenzoyl)-4-aza-5a-androst-1-en-3-one;

17ß-(3-phenylbenzoyl)-4-aza-5a-androst-1-en-3-one;

17ß-(4-biphenyl)-4-aza-5a-androst-1-en-3-one;

17ß-(3-biphenyl)-4-aza-5a-androst-1-en-3-one;

17ß-(1-naphthyl)-4-aza-5a-androst-1-en-3-one;

17ß-(2-naphthyl)-4-aza-5a-androst-1-en-3-one;

17ß-(1-phenanthryl)-4-aza-5a-androst-1-en-3-one;

17ß-(2-phenanthryl)-4-aza-5a-androst-1-en-3-one;

17ß-(1-biphenyl)-4-aza-5a-androst-1-en-3-one;

17ß-(9-anthracyl)-4-aza-5a-androst-1-en-3-one;

17ß-(4-thiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3-thiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-methylthiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-methylsulfinylphenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-methylsulfophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3-methylsulfinylphenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-N,N-dimethylaminosulfophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(2-ethyl-4-methylthiophenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-thioethylphenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-acetoxymethylthiophenylcarbonyl)-4-aza-4-methyl5α-androst-1-en-3-one;

17ß-(2-methyl-4-methylthiophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(2-methyl-4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(2-isopropyl-4-methylsulfophenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-methylthiophenylcarbonyl)-4-aza-4-methyl-5α-androstan-3-one;

17ß-(4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5α-androstan-3-one;

17ß-(4-methylsulfophenylcarbonyl)-4-aza-4-methyl-5α-androstan-3-one;

17ß-(4-hydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3-hydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3,4-dihydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-hydroxymethylphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(2-hydroxyethylphenylcarbonyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-methoxyphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-carboxymethylphenyl)-4-aza-5α-androst-1-en-3-one;

17ß-(4-hydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(3-hydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(3,4-dihydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-hydroxymethylphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(2-hydroxyethylphenylcarbonyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-methoxyphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17ß-(4-carboxymethylphenyl)-4-aza-4-methyl-5α-androst-1-en-3-one; and

17ß-(4-carboxyphenyl)-4-aza-5α-androst-1-en-3-one.

4. The method of Claim 1 wherein said compound of structure I is orally administered.

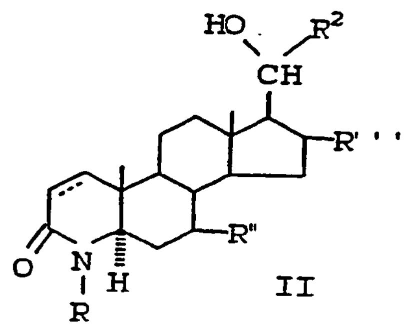
5. The method according to Claim 1 wherein the compound is administered at a daily dosage per person of from 1 to 2,000 mg.

6. The method according to Claim 5 wherein the compound is administered at a daily dosage per person of from 1 to 20 mg.

7. The method according to Claim 1 wherein said minoxidil is topically applied to the scalp in a concentration of about 1-5% by weight of an inert vechile adapted for topical application.

8. A topical pharmaceutical composition for the treatment of patterned alopecia comprising a therapeutically effective amount of minoxidil and a compound of the structural formula I as defined in Claim 1, in a vehicle adapted for topical application.

9. The method of Claim 1 wherein the compound is further of the structure:



II

wherein the dotted line can be a double bond when present,

R" and R''' are independently hydrogen or methyl;

R is selected from hydrogen, methyl and ethyl and

$R^2$ is
(a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of $C_1$-$C_2$ alkyl or halo;
(b) an aralkyl radical selected from benzyl or phenethyl;
(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, -O$C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkyl, halo or nitro;
(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, $-OC_1-C_4$ alkyl, $C_1-C_4$ alkyl, $-(CH_2)_mOH$, $-(CH_2)_n$ COOH, including protecting hydroxy, where m is 1-4, n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, $-SC_1-C_4$ alkyl, $-SOC_1-C_4$ alkyl, $-SO_2C_1-C_4$ alkyl, $-SO_2N(C_1-C_4\text{-alkyl})_2$, $C_1-C_4$ alkyl $-(CH_2)_mSH$, $-S-(CH_2)_n-O-COCH_3$, the where m is 1-4 n is 1-3, providing $C_1-C_4$ alkyl is only present when one of the above sulfur containing radicals is present;

(3) $N(R^3)_2$, which can be protected, where $R^3$ is independently H or $C_1-C_4$ alkyl, where the monoaryl ring can also be further substituted with $C_1-C_4$ alkyl; and

(e) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl; and pharmaceutically acceptable salts or esters thereof.

**Patents Act 1977**
**F··aminer's report to the Comptroller under Section 17**
**(. .e Search report)**

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**Relevant Technical Fields**

(i) UK Cl (Ed.M) A5B (BFC)

(ii) Int Cl (Ed.5) A61K 7/06

Search Examiner
J F JENKINS

Date of completion of Search
28 MARCH 1994

**Databases** (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASES: DIALINDEX (MEDICINE, WPI) CAS-ONLINE

Documents considered relevant following a search in respect of Claims :-
1 TO 9

**Categories of documents**

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

| Category | Identity of document and relevant passages | | Relevant to claim(s) |
|---|---|---|---|
| A | EP 0285382 A2 | (MERCK) | |
| Y | WO 92/02225 A1 | (UPJOHN) see Claim 10 | 1 and 3 |
| Y | US 4377584 | (MERCK) see Claim 12, column 1 lines 18-24, lines 42-45 and lines 64-66, column 3 line 51 Example Numbers 5 and 6 in Table | 1 and 3 |

**Databases:** The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).

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